

Association between environmental allergen sensitization with severity of atopic dermatitis in children and young adult at Dr. Sardjito General Hospital, Yogyakarta

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ABSTRACT

The important role of aeroallergens and food allergens as the most common environmental allergens in exacerbation of atopic dermatitis (AD) is well known. Sensitization is an essential process which correlates with clinical manifestation of AD. The study of AD in Indonesia, especially in Yogyakarta, has not been reported, yet. The aim of study is to evaluate the association between sensitization of environmental allergens with clinical severity of AD in children and young adult at Dr. Sardjito General Hospital, Yogyakarta. An analytic observational cross sectional study was performed on 33 children and young adult with AD. The severity of disease was determined by SCORing Atopic Dermatitis (SCORAD). Assessment of sensitization was performed using specific IgE serum, atopy patch test, and prick test. Data were analyzed using chi-square or Fisher exact test and prevalence ratio (PR) with significance value of $p < 0.05$ and 95% confidence interval (CI). The results showed that specific IgE positivity was associated with severity of AD. Percentage of specific IgE positivity to house dust mite was significantly higher in subject with moderate/severe AD compared to those of mild AD ($p = 0.049$; PR 1.13; 95% CI 1.01-1.59). The result was also similar for cat dander ($p = 0.041$; PR 1.1; 95% CI 1.09-4.98), cow's milk ($p = 0.038$; PR 1.21; 95% CI 1.02-2.2), and egg white ($p = 0.027$; PR 1.23; 95% CI 1.15-2.97). Whereas specific IgE positivity to fish allergen was not statistically different in subject with moderate/severe AD compared to those with mild AD ($p = 0.061$; PR 0.8; 95% CI 0.76-2.8). According to atopy patch test and prick test result, no association was found between allergen sensitization and severity of AD. If all methods were combined to increase the sensitivity of sensitization measurement, then the association was found for all allergens. It could be concluded that environmental allergens sensitization is associated with severity of AD in children and young adult at Dr. Sardjito General Hospital, Yogyakarta.

Key words: atopic dermatitis-disease severity-sensitization-aeroallergen-food allergen

INTRODUCTION

Atopic dermatitis (AD) is a chronic and recurrent inflammatory skin disease that occurs especially in infants and children, but can also be found in adulthood. The etiology is still unknown. The pathogenesis is complex and involves many factors, makes AD is described as a multifactorial disease. The prevalence of AD has increased more than threefold since 1960 and became a worldwide health problem.¹

The role of allergy in the pathogenesis of AD is still controversial. However, it is known that exposure to environmental allergens can stimulate

the emergence of AD lesion. Environmental allergens that most frequently involved in the pathogenesis of AD are food and aeroallergens.²

Sensitization is an important step in the pathogenesis of AD. This sensitization of allergens can occur through the skin or inhalation. Several epidemiological studies have been started to evaluate the association between the degree of severity with allergen sensitization of AD, but the results were varied and sometimes were controversial. It was assumed that in AD patients who have experienced sensitization, the concentration of antibody immunoglobulin E (IgE) specific to aeroallergens

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was associated with the severity of AD.²⁻⁴ Study of AD in Indonesia, especially in Yogyakarta, has not been reported, yet.

The study aimed at exploring the association between environmental allergens sensitization with the severity of AD in children and young adult at Dr. Sardjito General Hospital Yogyakarta, Indonesia.

MATERIALS AND METHODS

This study was conducted at the Outpatient Clinic of Department of Dermatovenereology, Faculty of Medicine, Gadjah Mada University/Dr. Sardjito General Hospital Yogyakarta, commencing in September 2009 until reach the number of 33 subjects. A cross sectional analytic observational study was designed.

The inclusion criteria were men or women between the ages 2-25 years with AD in which the diagnosis was based on the criteria of Hanifin Rajka, had lived in Yogyakarta for a minimum of two years, subjects or parents understood the procedures and side effects that might occur during the procedures, and agreed to participate in this study. The exclusion criteria were subjects on systemic immunomodulatory therapy within the last four weeks before study, subjects in topical corticosteroid therapy within the last four weeks before study, and subjects taking systemic antihistamines at least one week before study.

Sensitization was measured by using three methods, IgE specific (Euroline® system), atopy patch test and prick test to house dust mites (*Dermatophagoides pteronyssinus*), cat dander, egg white, cow's milk and fish. Measurement of sensitization was considered "positive" if IgE specific level was >0.35 kU/I (RAST class 1) or prick test result showed diameter of wheal e"3 mm or at least ½ diameter of positive control or atopy patch test result showed positive 1 to positive 4 reaction according to *European Task Force of Atopic Dermatitis* (EFTAD).

Degree of severity of AD was determined by *SCORing Atopic Dermatitis* (SCORAD). Data were analyzed using non-parametric test of chi-square or Fisher with a significance of p<0.05, prevalence ratio (PR) with 95% confidence interval (CI).

This study has been approved by The Medical and Health Research Ethics Committee of Faculty of Medicine, Gadjah Mada University, Yogyakarta.

RESULTS

Thirty three subjects participated in this study and fulfilled the inclusion criteria. They were categorized into 2 groups, 4 (12.1%) subjects with mild AD and 29 (87.8%) subjects with moderate to severe AD (moderate/severe). The characteristic of subjects is shown in TABLE 1.

TABLE 1. Characteristic of subjects

Characteristic	AD n (%)		Total n (%)	p value
	Mild	Moderate/ Severe		
Sex				
- Male	3 (9)	16 (24.2)	19 (57.6)	0.17
- Female	1 (3)	13 (24.2)	14 (42.4)	
Age				
- Mean	11.1	9.05	9.19	0.56
- SD (range values)	6.47	3.74	4.39	
Other atopic diseases				
- None	1 (3)	9 (27.3)	10 (30.3)	0.27
- Exist	3 (9)	20 (60.6)	23 (69.7)	
- Asthma	4 (12.1)	11(33.3)	15 (45.5)	
- Allergic rhinitis	3 (9)	18 (54.5)	21 (63.6)	
- Asthma & Allergic rhinitis	3 (9)	8 (24.2)	10 (28.6)	
Atopic family history				
- None	0 (0)	0 (0)	0 (0)	0.21
- Exist	4 (12.1)	29 (87.9)	33 (100)	

The mean value of SCORAD was 49.19 ± 14.87 (16.04 to 81.27). Test of homogeneity of gender, age, other atopic diseases and atopic diseases in the family showed no significant difference.

Distribution of allergen sensitization according to specific IgE, prick test and atopy patch test can be seen in FIGURE 1.

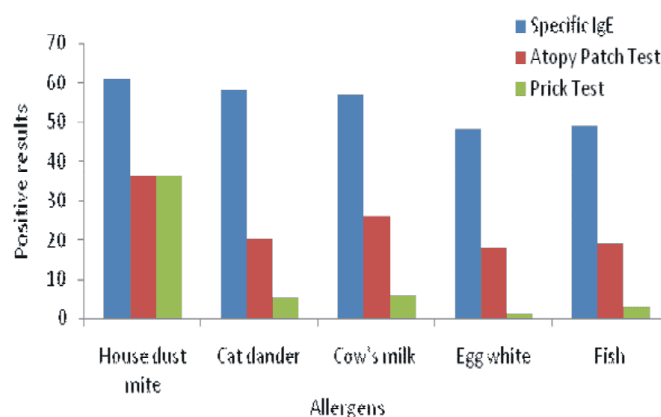


FIGURE 1. Distribution of sensitization test to 5 allergens according to three methods

The majority of positive result was demonstrated by specific IgE, followed by atopy patch test and prick test. House dust mite (60.6%, 36.4%, and 36.4%) was found as the most common allergens. Specific IgE positivity was associated with severity of AD (TABLE 2). Percentage of specific IgE positivity to house dust mite was significantly

higher in subject with moderate/severe AD compared to those of mild AD ($p=0.049$; PR 1.13; 95% CI 1.01-1.59). The result was also similar for cat dander ($p=0.041$; PR 1.1; 95% CI 1.09-4.98), cow's milk ($p=0.038$; PR 1.21; 95% CI 1.02-2.2), and egg white ($p=0.027$; PR 1.23; 95% CI 1.15-2.97).

TABLE 2. Association between environmental allergen sensitization according to specific IgE with severity of AD

Specific IgE	Severity of AD n (%)		p value	PR (95% CI)	
	Moderate/Severe	Mild			
House dust mite	Positive	18 (54.5)	2 (6)	0.049*	1.13 (1.01-1.59)
	Negative	11 (33.3)	2 (6)		
Cat dander	Positive	17 (54.5)	2 (6)	0.041*	1.10 (1.09-4.98)
	Negative	12 (33.3)	2 (6)		
Cow's Milk	Positive	18 (54.5)	0 (0)	0.027*	1.21 (1.02-2.2)
	Negative	11 (33.3)	4 (12.1)		
Egg White	Positive	13 (39.3)	2 (6)	0.036*	1.23 (1.15-2.97)
	Negative	16 (48.5)	2 (6)		
Fish	Positive	13 (39.6)	3 (9)	0.061	0.8 (0.76-2.8)
	Negative	16 (48.5)	1 (3)		

* $p < 0.05$ Fisher exact test; PR=prevalence ratio; CI=confidence interval

According to atopy patch test, no association was found between allergen sensitization and severity of AD (TABLE 3). Percentage of atopy patch test positivity to house dust mite was not significantly higher in subject with moderate/severe AD compared to those of mild AD (p=0.095; PR

0.92; 95% CI 0.97-2.84). The result was also similar for cat dander (p=0.256; PR 0.97; 95% CI 0.95-2.55), cow's milk (p=0.491; PR 1.02; 95% CI 0.07-1.69), egg white (p=0.096; PR 0.93; 95% CI 0.14-3.45), and fish (p=0.581; PR 0.581; 95% CI 0.75-1.95).

TABLE 3. Association between environmental allergen sensitization according to atopy patch test with severity of AD

Specific IgE	Severity of AD n (%)		p value	PR (95% CI)
	Moderate/Severe	Mild		
House dust mite	Positive	10 (30.2)	0.095	0.92 (0.97-2.84)
	Negative	19 (57.6)		
Cat dander	Positive	6 (18.1)	0.256	0.97 (0.95-2.55)
	Negative	23 (69.7)		
Cow's Milk	Positive	8 (24.1)	0.491	1.02 (0.07-1.269)
	Negative	21 (60.7)		
Egg White	Positive	5 (15.0)	0.096	0.93 (0.14-3.45)
	Negative	24 (72.7)		
Fish	Positive	6 (18.0)	0.581	0.98 (0.75-1.95)
	Negative	23 (69.7)		

PR=prevalence ratio; CI=confidence interval

According to prick test, no association was found between allergen sensitization and severity of AD (TABLE 4). Percentage of prick test positivity to house dust mite was not significantly higher in subject with moderate/severe AD compared to those

of mild AD (p=0.097; PR 1.07; 95% CI 0.11-1.41). The result was also similar for cat dander (p=0.769; PR 1.15; 95% CI 0.82-1.31), cow's milk (p=0.670; PR 1.15; 95% CI 0.77-2.01), and fish (p=0.879; PR 1.15; 95% CI 0.039-1.3).

TABLE 4. Association between environmental allergen sensitization according to prick test with severity of AD

Specific IgE	Severity of AD n (%)		p value	PR (95% CI)
	Moderate/Severe	Mild		
House dust mite	Positive	11 (63.6)	0.097	1.07 (0.11-1.41)
	Negative	18 (24.2)		
Cat dander	Positive	2 (6)	0.769	1.15 (0.82-1.31)
	Negative	27 (81.8)		
Cow's Milk	Positive	3 (9)	0.670	1.15 (0.77-2.01)
	Negative	26 (78.8)		
Egg White	Positive	0 (0)	NA	NA
	Negative	29 (57.6)		
Fish	Positive	1 (100)	0.879	1.15 (0.04-1.30)
	Negative	28 (84.9)		

NA= not available; PR=prevalence ratio; CI=confidence interval

If all of those three of methods (IgE specific, atopy patch test and prick test) were combined to increase the sensitivity of sensitization test, the

association between environmental allergen sensitization with severity of AD is demonstrated in TABLE 5.

TABLE 5. Association between environmental allergen sensitization according to sensitization test with severity of AD

Specific IgE/atopy Patch test/Prick Test [†]	Severity of AD n (%)		p value	PR (95% CI)	
	Moderate/Severe	Mild			
House dust mite	Positive	22 (66.7)	3 (9)	0.032*	1.09 (1.07-2.99)
	Negative	7 (21.2)	1 (3)		
Cat dander	Positive	20 (60.60)	2 (6)	0.046*	1.12 (1.05-3.72)
	Negative	9 (27.3)	2 (6)		
Cow's Milk	Positive	20 (60.6)	2 (6)	0.046*	1.12 (1.05-3.72)
	Negative	9 (27.3)	2 (6)		
Egg White	Positive	16 (48.3)	3 (9)	0.049*	1.08 (1.02-3.21)
	Negative	13 (39.4)	1 (3)		
Fish	Positive	15 (45.5)	3 (9)	0.048*	1.23 (1.01-2.36)
	Negative	14 (42.4)	1 (3)		

* $p < 0.05$ Fisher exact test; PR=prevalence ratio; CI=confidence interval,

[†]Positive sensitization define by positive result in one of three sensitization methods (specific IgE >0.35 kU/I OR diameter of prick test' wheal e"3 mm or at least 1/2 diameter of positive control OR atopy patch test showed +1 to +4 reaction)

According to combination of three methods (IgE specific, atopy patch test and prick test) for parameter of sensitization, association was found between environmental allergen sensitization and severity of AD (TABLE 8). Percentage of specific IgE positivity or atopy patch test positivity or prick test positivity to house dust mite was significantly higher in subject with moderate/severe AD compared to those of mild AD ($p=0.031$; PR 1.09; 95% CI 1.07-2.99). The result was also similar for cat dander ($p=0.046$; PR 1.12; 95% CI 1.05-3.72), cow's milk ($p=0.046$; PR 1.12; 95% CI 1.05-3.72), egg white ($p=0.049$; PR 1.08; 95% CI 1.02-3.21), and fish ($p=0.048$; PR 1.23; 95% CI 1.01-2.36).

DISCUSSION

This study involved thirty three subjects of children and young adults with AD in various degree of severity. They were categorized into 2 groups, those with mild AD and those with moderate/severe AD based on differences in risk of complication and management.^{5,6}

The results of this study indicated that most of sensitizations were found to aeroallergen (house dust mites), followed by food allergen (cow's milk) (FIGURE 1). The percentage of positive results in the sensitization test to aeroallergens was higher than food allergens in this study because the mean age of subjects was 9.19 years in which the pattern of

sensitization has been largely influenced by aeroallergens.^{7,8}

House dust mite species were mostly found in the environment, namely *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Der f).⁹ Many studies focused on Der p 1 as the most commons allergens that were found in high concentrations in mite faeces. *Dermatophagoides pteronyssinus* is important in the pathogenesis of AD because it shows high cysteine protease activity, therefore Der p 1 has IgE binding capability of 80-100% and it also has the ability to induce Th2 cytokine production. High titer of specific antibodies of Der p 1 was found in 95% AD and was correlated with disease severity.^{7,9-11}

Schafer *et al.*¹² suggested that the level of sensitization in AD influenced the occurrence of skin manifestations and affected the severity of disease with a linear pattern. The results of this study indicated that the association between environmental allergen sensitization as shown by specific IgE levels with the severity of AD was found (TABLE 2). These results were also consistent with Katoh *et al.*¹³ which showed that AD with high specific IgE values (> 17.5 kU/I) was associated with extensive area involvement after 10 years of evaluation.

The measurement of specific IgE is an objective examination with a higher reproducibility and considered as the most accurate sensitization method

compared to atopy patch test and prick test. Several studies had using specific IgE as the gold standard measurement of allergen sensitization.¹⁴⁻¹⁶ This method can be performed in cases where prick test are contraindication such as the presence of lesions in the test area or in conditions under drugs intervention.¹² In children, measurement of specific IgE is recommended because it is easy and less invasive than prick test and atopy patch test.^{16,17}

In this study, percentage of sensitization test positivity according to either one of atopy patch test or prick test was not significantly higher in subject with moderate/severe AD compared to those of mild AD. However, the number of atopy patch test and prick test positivity were higher in moderate/severe AD (TABLE 3 and 4). This result was consistent with Holm *et al.*⁷ and Laske *et al.*¹⁸ that sensitization to aeroallergens and food allergens are in line with severity of AD.

Atopy patch testing performed in this study was using prick test allergens produced by Dr. Indrayana, LAPI Jakarta. It was possible that the concentration of allergens was too low to induced sensitization. Optimal dose of aeroallergens which can induce skin reactions in atopy patch test is 5000-7000 units per gram of protein nitrogen in petrolatum.¹⁹ However, Shankar and Chakravarthi in 2008 also performed atopy patch testing by using aqueous prick test allergen with aeroallergen concentrations ranging from 1500-5000 per unit of protein nitrogen grams and food allergens at 1% w/v and the results showed that the application of prick test allergens to intact skin can cause skin reactions. Other causes which influenced the atopy patch test results in this study was the tendency of parents to bring their children to hospital in an acute state of AD was larger than those with a chronic state of AD. Atopy patch test is a test method based on delayed type of hypersensitivity reactions, therefore in most subjects this reaction has not occurred.²⁰

Prick test results in this study was not associated with the severity of AD, which was in line with Berger²¹ and Seinedari *et al.*²² that suggested that the prick test can not be used as a predictor of the severity of AD in children. Prick test reactivity was higher in patients more than 15 years old, while positive results on atopy patch test were more often found in patients less than 6 years old, but the reason for this was still unknown. This was accordance with

this study, where the average age of subjects was 9.19 years. Prick test also has positive predictive value of less than 40%, this suggested that individuals with a positive prick test results to certain allergens may not experience any disruption when exposed to these allergens.¹⁶

The results of this study indicated that when the three tests were used in a combination to increase the sensitivity, the percentage of sensitization test positivity became higher and statistically significant for all allergens (TABLE 5). This means that those methods are complementary, therefore that it is expected to increase the sensitivity of diagnostic tests.¹⁶ Complete process of sensitization would be obtainable by using combination of several methods of sensitization test. Specific IgE determines allergen specific IgE antibodies in the serum and, in contrast with SPT, gives a quantitative result of detected IgE antibodies which bind to the surface of mast cell, whereas atopy patch test represents T cell mediated delayed response of sensitization.²³⁻²⁵ Prick test and specific IgE measurement are important for determination of sensitization in AD, but the accuracy of those examination are reduced in the delayed type manifestation of allergic diseases, especially food allergies. In this case, atopy patch test is helpful in determining sensitization in AD.^{26,27}

The limitation of this study was the marked difference number of subject between mild AD (4/12.1%) and moderate/severe AD (29/87.8%) that may cause insignificant analysis. Another limitation of cross sectional design is that we can not conclude whether the sensitization precede the severity of AD or vice versa.

CONCLUSION

The results of this study concluded that the sensitization towards environmental allergens associated with severity of AD in children and young adults at Dr. Sardjito General Hospital, Yogyakarta.

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